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Radiocontrast-induced nephropathy in humans: Role of renal vasoconstriction

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Radiocontrast-induced nephropathy in humans: Role of renal vasoconstriction. Radiocontrast-induced nephropathy (RCIN) is a common cause of acute renal failure in hospitalized patients. Renal vasoconstriction figures prominently in the proposed pathogenesis of RCIN based on animal experiments. Prior human studies examining renal hemodynamic changes after contrast medium (CM) injection are inconclusive. No previous study of animals or humans has established a relationship between CM-associated renal hemodynamic changes and the subsequent development of RCIN. In the present study, we examined the renal hemodynamic effects of CM in patients at high risk of RCIN. In addition, we related those effects to the subsequent development of RCIN. Using renal vein thermodilution catheters, we measured renal blood flow (RBF) in 12 patients with chronic renal failure [serum creatinine (S_{Cr}) ≥ 159 μmol/liter] during ionic CM injection for cardiac catheterization. We made measurements at the start of the procedure (t = 0), before the ventriculogram (t = 5), after the ventriculogram (t = 15), and after the coronary angiogram (t = 65). We measured S_{Cr} at t = 0 and again 24 and 48 hours later. Mean RBF for the group tended to increase after the ventriculogram, and increased significantly by t = 65 ($P < 0.005$ vs. t = 0). When examined by individual patient, RBF fell below baseline in three patients (30%) at t = 15, but rose above baseline again by t = 65. Only one patient (8.3%) had a fall in RBF below baseline at t = 65. RCIN (defined as an increase in S_{Cr} ≥ 25% above baseline) developed in six patients (50%) within 48 hours. Of those only two (33%) had shown a fall in RBF at t = 15, and none at t = 65. Of the four patients in the group as a whole whose RBF had fallen at any time, only two (50%) developed RCIN. We conclude that intracardiac injection of ionic CM is not associated with a fall in total RBF in most patients with chronic renal failure. Furthermore, there appears to be no relationship between the development of RCIN and any change in total RBF. Global renal vasoconstriction does not appear to play a pathogenic role in RCIN in humans with chronic renal failure.

Radiocontrast induced nephropathy (RCIN) is an important cause of acute renal failure [1, 2]. Pre-existing renal insufficiency increases the risk of developing RCIN [3–7]. Therapeutic maneuvers designed to reduce the risk of RCIN in humans thus far have been disappointing. In particular, a beneficial effect of non-ionic contrast medium (CM) has not been clearly demonstrated [3–5, 8, 9].

The rational development of effective prophylactic regimens for RCIN will depend on a complete understanding of its pathogenesis. Prominent among the current pathogenic formulations is the role of renal vasoconstriction [10, 11]. This proposed mechanism owes its popularity to a number of studies in animals [12–17] showing an abrupt increase followed by a decrease in global renal blood flow (RBF) after CM injection.

Whether CM has such a renal hemodynamic effect in humans is not clear. Most data in this area derive from studies in humans using para-amino hippurate (PAH) infusion to estimate RBF [18–21], a method of questionable validity in the presence of iodinated CM [20, 22, 23]. Studies using other RBF measurement techniques in humans are few and contradictory [24, 25].

There are four "multiple insult" animal models of RCIN [26–29], however, none of the data derived from them permits any inference about the pathogenic role of contrast-induced renal hemodynamic changes. In human experiments, changes in RBF during CM infusion have never been correlated with the subsequent development of RCIN.

We therefore designed the present study to answer two questions: (1) Is intravascular CM injection associated with an immediate decrease in global RBF in humans? and, if so, (2) Is there a relationship between immediate contrast-induced renal vasoconstriction and the subsequent development of RCIN? We chose to study a population of patients we have previously shown to be at high risk for RCIN: patients with chronic renal insufficiency undergoing cardiac catheterization [7]. We measured changes in global renal blood flow during cardiac catheterization using a renal vein thermodilution catheter. In addition we monitored renal function in these same patients for several days to detect the development of RCIN. Our results demonstrate that CM injection is not predictably associated with global renal vasoconstriction in humans with chronic renal insufficiency, and that there is no relationship between global renal vasoconstriction and the subsequent development of RCIN.

Methods

Patient selection

All patients with chronic renal failure, defined as a stable serum creatinine concentration (S_{Cr}) greater than or equal to 159 μmol/liter (1.8 mg/dl), undergoing elective cardiac catheterization were considered eligible for inclusion in the study. Patients were specifically excluded if they had New York Heart Association Class IV congestive heart failure, hepatic disease, hemodynamic instability, allergy to CM, prior CM exposure

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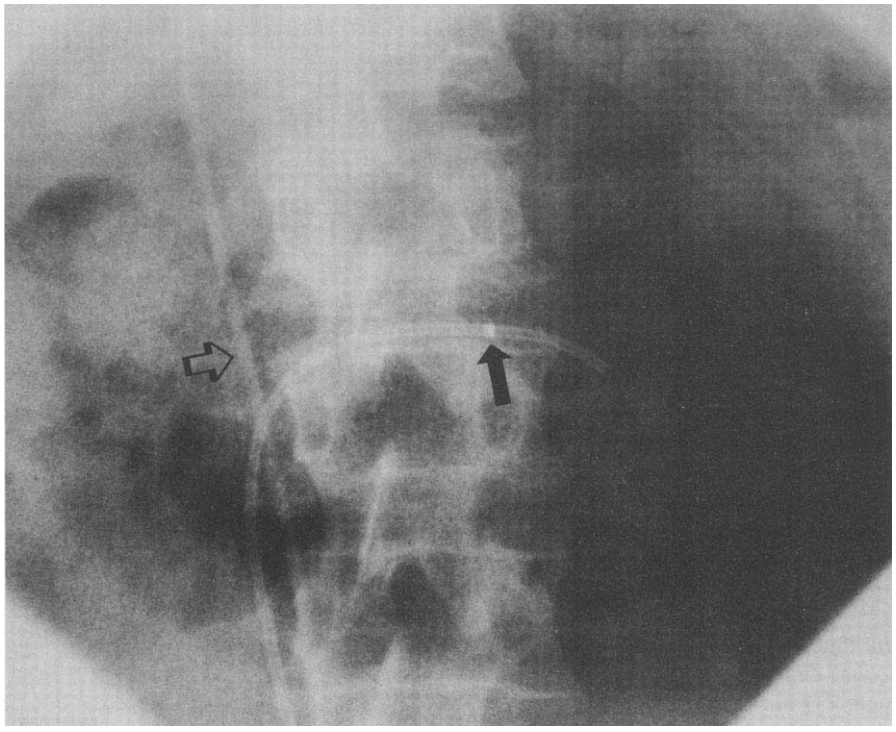

Fig. 1. *Radiograph showing thermodilution catheter in the left renal vein (solid arrow).* A Swan-Ganz catheter is seen in the inferior vena cava (open arrow). Note that the thermistor (tip of solid arrow) lies well within the renal vein.

within seven days of the experimental protocol, or were pregnant. Before enrollment in the study all patients gave informed written consent to participate in the research protocol approved by the Institutional Review Board at Cooper Hospital/University Medical Center. A medical history was taken and a physical examination performed with specific attention to the exclusion criteria, medications and the etiology of chronic renal failure.

Experimental protocol

All patients had S_{Cr} measured upon entry into the study. Intravenous 75 mM sodium chloride was infused at 100 ml/hr beginning 12 hours before, and continuing throughout, the cardiac catheterization. At no time did patients receive mannitol. Cardiac catheterization was performed by the percutaneous femoral approach in the fasting state. One arterial and two venous sheaths were placed and baseline S_{Cr} was measured (time 0, t = 0). A catheter was advanced into the left renal vein for serial measurements of RBF (see below). A Swan-Ganz thermodilution catheter was advanced into the pulmonary artery for serial determinations of cardiac output and right heart pressures. A pigtail catheter was advanced into the left ventricle for ventriculography. All patients underwent a single ventriculogram (completed by about 15 minutes, t = 15) followed by coronary angiography (completed by about 65 minutes, t = 65). The CM used in all cases was MD76 (66% diatrizoate meglumine, 10% diatrizoate sodium). A record was made of all hemodynamic changes and medications administered during the catheterization as well as the total volume of CM infused.

Measurement of renal blood flow

RBF was measured using a 7-French dual thermistor thermodilution catheter (Webster Labs, Baldwin Park, California, USA) introduced through the femoral vein via an indwelling introducer and fluoroscopically guided into the left renal vein. We chose to catheterize the left renal vein since it is longer than the right, about three times as long as the distance from the tip of the thermodilution catheter to the external thermistor. In this way, we ensured that the external thermistor remained well within the renal vein throughout the protocol (Fig. 1). The position of the catheter in the renal vein was confirmed by documenting a step-up in oxygen saturation of blood withdrawn through the catheter. We documented saturation greater than 80% in all cases, confirming position in the renal vein [30]. In addition, we checked the position of the catheter fluoroscopically several times during each protocol. We used a continuous thermodilution technique for RBF determinations as reported previously [7]. Room-temperature 5% dextrose was infused through the catheter with a Harvard pump (Harvard Apparatus Co., Millis, Massachusetts, USA) at a constant rate of 50 ml/min until the deflections of both thermistors consequent to the thermodilution temperature changes were stable. This method has been shown to accurately and reproducibly measure momentary increases and decreases in renal blood flow [7, 30–32]. Three or four replicate RBF measurements were made at approximately one-minute intervals for each time point. In one patient, we measured RBF nine times between 20 seconds and eight minutes following the ventriculogram. RBF was measured at t = 0, t = 5 (before the ventriculogram), t = 15 (immediately after the ventriculogram), and t = 65 (after the coronary angiogram).

Laboratory measurements

A blood specimen for S_{Cr} was obtained upon entry into the study. S_{Cr} measurement was repeated at t = 0, 24 hours after

Table 1. Baseline patient characteristics

Patient	Age	Sex	S_{Cr} *μmol/liter*	CC_{Cr} *ml/min*	Disease[a]	Medications[b]
#1	80	F	203	11	RhHD	prop, ISDN
#2	60	M	239	40	ADPKD	ISDN
#3	72	M	168	34	CHF	ver, furos, dig
#4	68	M	248	34	HTN	metop, nifed
#5	64	F	327	16	DM, HTN	nicard, bumet
#6	72	F	301	17	DM, HTN	dilt, ISDN
#7	54	M	168	52	HTN	labet, dilt
#8	70	M	292	27	DM, HTN	dilt, ISDN
#9	76	F	212	18	HTN, CHF	dilt
#10	73	F	301	18	DM	ASA
#11	59	F	274	19	DM, HTN	furos, nifed
#12	63	M	203	36	DM	dig, ver
Mean	67.6		248	26.7		
SEM	2.2		18	3.6		

Abbreviations are: S_{Cr}, serum creatinine concentration; CC_{Cr}, calculated creatinine clearance, according to the formula of Cockcroft and Gault [33].

[a] RhHD, rheumatic heart disease; ADPKD, autosomal-dominant polycystic kidney disease; HTN, hypertension; DM, diabetes mellitus; CHF, congestive heart failure.

[b] prop, propranolol; ISDN, isosorbide dinitrate; ver, verapamil; furos, furosemide; dig, digoxin; metop, metoprolol; nifed, nifedipine; nicard, nicardipine; bumet, bumetanide; dilt, diltiazem; labet, labetalol; ASA, aspirin.

the catheterization and daily thereafter until the S_{Cr} value returned to the baseline level or stabilized. S_{Cr} was determined by a modified Jaffe end-point assay in an Hitachi 737 autoanalyzer (Boehringer-Manheim, Indianapolis, Indiana, USA). We defined RCIN as a rise in S_{Cr} of at least 25% 48 hours after the cardiac catheterization.

Statistical analysis

All continuous data were tabulated and analyzed as mean ± SEM. Paired *t*-tests were used to determine differences between two time points. Differences were considered to be significant when P was less than 0.05.

Results

Clinical characteristics

Twelve patients met the study criteria for enrollment and completed the described protocol. The clinical characteristics of the patients are shown in Table 1. Nine of the 12 patients were taking calcium channel blockers on a long-term basis. The mean total dose of CM was 145.1 ± 11.6 ml, the ventriculogram accounting for 28 to 45 ml of that amount.

Renal and systemic hemodynamics

The mean coefficient of variation for all replicate RBF measurements in our laboratory is 9.1%. The mean coefficient of variation at low RBF (<200 ml/min) was not significantly different than at high RBF (≥200 ml/min) (8.5 ± 0.9% vs. 10.1 ± 0.8%, respectively, $P = 0.24$). All patients had RBF measurements made at t = 0, t = 5 and t = 65. Two patients (#9 and #11) did not have RBF measured at t = 15 for technical reasons.

Figure 2 shows mean percent change in RBF for all patients over time. RBF tended to rise after the ventriculogram (121 ± 53%), and the increase reached significance after the coronary angiogram (176 ± 94%, $P < 0.005$ vs. t = 0). Figure 3 shows absolute RBF by individual patient over time. Compared with the t = 0 value, RBF rose or remained constant in all but three patients (#3, #5 and #7) immediately following the ventriculogram (t = 15). In those three patients, RBF fell by 16%, 13% and 16%, respectively. If t = 5 is taken as the baseline, no patient sustained a fall in RBF after the ventriculogram. At t = 65, after coronary angiography, only one patient (#12) showed a decline in RBF (by 19%) compared with the measurement at t = 0 or t = 5. Of the patients who were taking no calcium channel blocker (#1, #2 and #10), none had a fall in mean RBF below baseline at any time point.

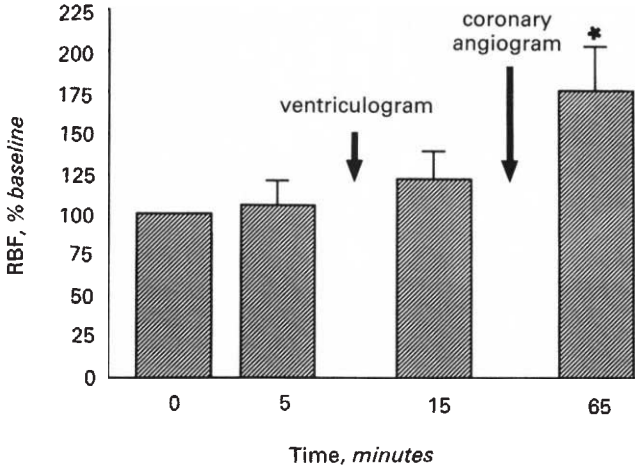

Fig. 2. *Mean percent change in RBF during cardiac catheterization for all patients.* Mean RBF at t = 0 is 100%. *$P < 0.05$ vs. t = 0 (paired *t*-test).

Figure 4 shows the actual replicate measurements made for each patient following the ventriculogram. The ventriculogram was performed at t = 15 and the replicate measurements made at approximately one-minute intervals beginning less than one minute after CM injection. One patient (#12) had nine separate measurements made over eight minutes beginning 20 seconds after CM injection. RBF tended to remain stable after exposure to a discrete injection of CM.

The average mean arterial pressure (MAP) at baseline was 108 ± 13 torr and remained constant throughout the protocol,

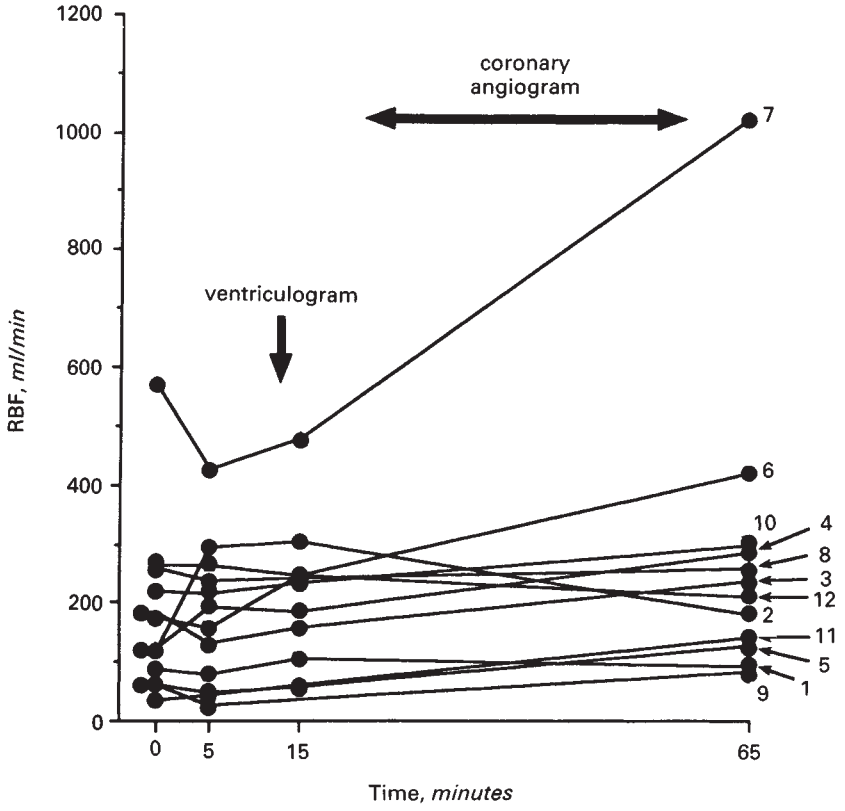

Fig. 3. *Absolute RBF during cardiac catheterization, by individual patient.* Line labels at right correspond to patient number in Table 1. Ventriculogram was performed at approximately t = 14. Coronary angiogram was performed between approximately t = 20 and t = 60. Each point represents the mean of three or four replicate RBF measurements made within approximately one minute of each other.

except for the usual transient dip in MAP immediately after CM injection for both the ventriculogram and coronary angiography, lasting less than 30 seconds [34]. In all cases but one (#12, after the ventriculogram) RBF measurements were made more than 30 seconds after the CM injection, when MAP had returned to baseline. Mean cardiac output for the group at baseline was 4.61 ± 1.2 liter/min and remained constant until t = 65 at which time it rose to 5.1 ± 1.5 liter/min ($P < 0.05$ vs. t = 0). Mean renal vascular resistance (calculated as RVR = (MAP − RAP) ÷ RBF, where RAP is right atrial pressure) at t = 65 was 67 ± 7% of the mean baseline value, a significant decline ($P < 0.001$).

Serum creatinine concentration

Figure 5 shows S_{Cr} at baseline and 48 hours after cardiac catheterization. S_{Cr} rose by more than 25% in six of the 12 patients (#1, #3, #4, #5, #8, #11). Three patients, all of whom had diabetes mellitus, required dialysis (#5, #8, #11). Of the six patients who developed RCIN, two (#3, #5) had shown a significant decrease below baseline RBF after the ventriculogram, however, RBF for all six patients who developed RCIN was at or above baseline at t = 65 (Fig. 6). Of the four patients in the group as a whole whose RBF fell with respect to baseline at any time after radiocontrast infusion, only two developed RCIN (#3 and #5).

Discussion

We studied the global renal hemodynamic effects of CM injection in patients at high risk of developing RCIN: patients with chronic renal insufficiency. In addition, we attempted to define the relationship between global renal hemodynamics following CM injection and the subsequent development of RCIN in this high-risk population.

Our results demonstrate clearly that intracardiac ionic radiocontrast medium does not tend to cause a decrease in overall RBF in humans with impaired renal function. On the contrary, mean RBF for the group as a whole increased after exposure to CM (Fig. 2).

Most of the data derived from animal experiments indicate maximal vasoconstriction at about 40 seconds after CM injection. The duration of the vasoconstriction is highly variable, lasting from one minute after a single injection [12–16] to over 3½ hours after repeated contrast injections [17]. Studies in humans have shown a decrease in PAH extraction or clearance lasting between two and 60 minutes [18–21]. The magnitude of the reported decrease ranges between 10 and 50 percent, the most common decrement being about 20 percent, well within the range detectable by the thermodilution method [7, 30–32].

To examine the immediate effect of a discrete CM injection on RBF we analyzed the individual replicate RBF measurements made at approximately one minute intervals following the ventriculogram (Fig. 4). RBF remained essentially stable and unchanged from the pre-injection level. A significant momentary hemodynamic perturbation might have occurred within the first minute; however, we noted no such effect in the one patient whose RBF was measured beginning 20 seconds after CM injection. Thus, a discrete intracardiac injection of ionic CM was not associated with global renal vasoconstriction in this population.

Mean RBF was significantly higher at t = 65 than at baseline,

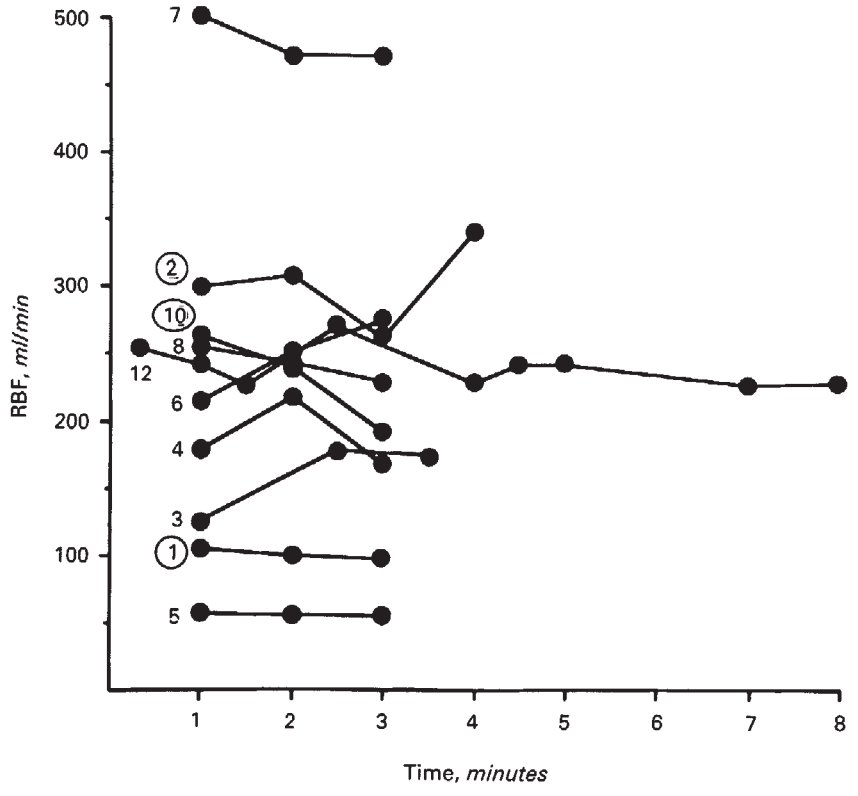

Fig. 4. *Absolute RBF over time, by individual patient, immediately following the ventriculogram (at 0 min).* Line labels at left correspond to patient number in Table 1. Circled numbers refer to patients taking no calcium channel blockers. Each point represents a single RBF measurement.

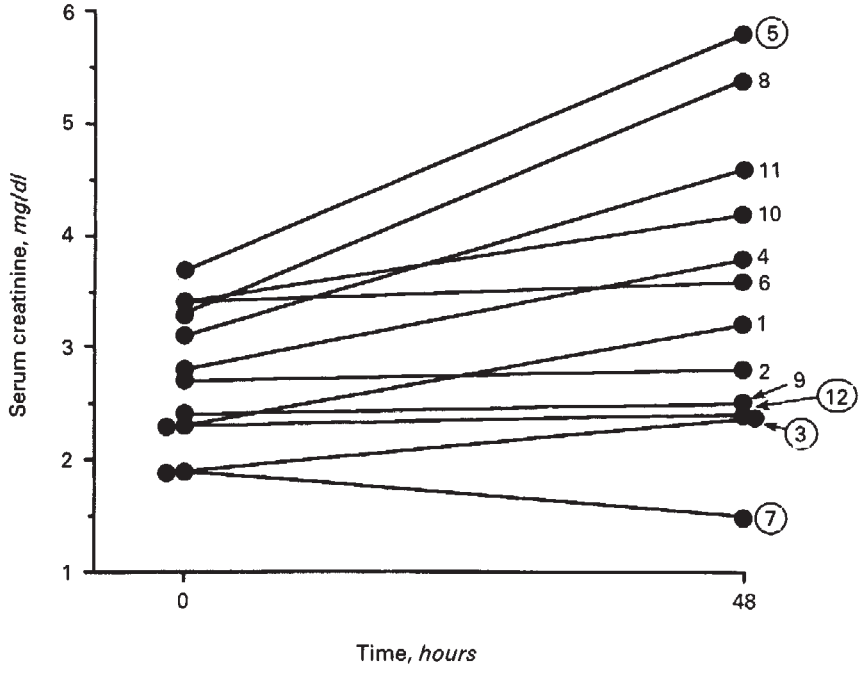

Fig. 5. *Change in serum creatinine concentration after cardiac catheterization, by individual patient.* Time 0 hours corresponds to t = 0 in Figures 1 and 2. Line labels at right correspond to patient numbers in Table 1. Circled numbers refer to patients whose RBF fell below baseline at any time after contrast medium injection.

and when analyzed by individual patient RBF rose or remained constant in 11 of 12 patients (92%). Thus repeated injections of CM did not cause global renal vasoconstriction.

Half the patients developed RCIN by our criterion. This is similar to the incidence we [7] and others [6] have reported previously in comparable "high-risk" patients. If global renal vasoconstriction were important in the pathogenesis of RCIN we would have expected those patients whose S_{Cr} rose to have shown a fall in overall RBF below their baseline after CM injection. In fact, however, of the six patients whose S_{Cr} rose, only two had a transient decrease in RBF after the ventriculogram, and none showed a fall below baseline at t = 65 (Fig. 6).

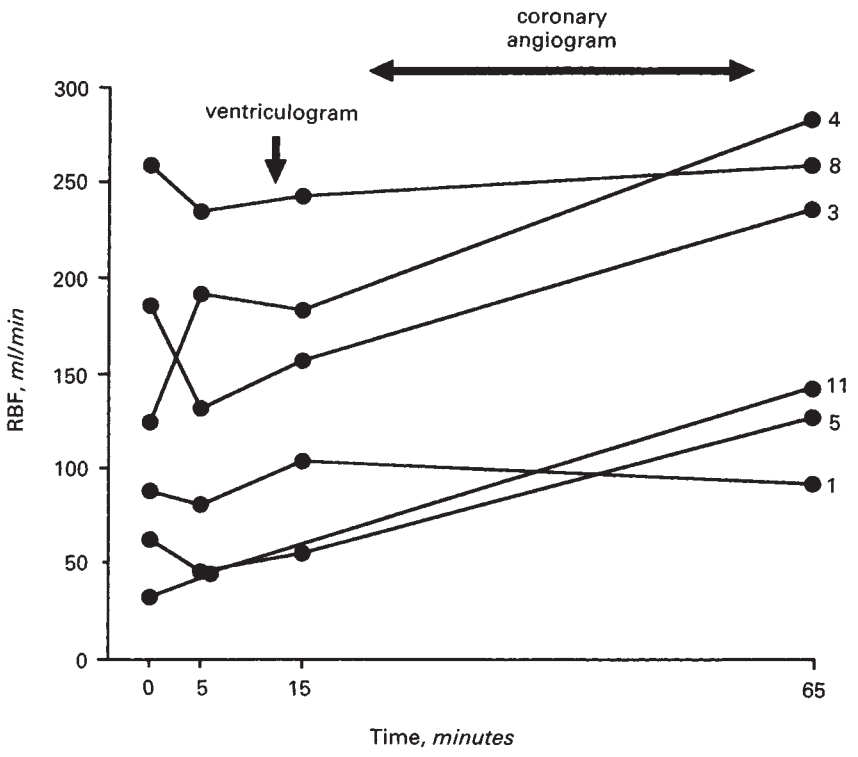

Fig. 6. *Absolute RBF over time in patients who developed RCIN.* See Figure 3 legend for details. Patient #11 had no measurement of RBF at t = 15 for technical reasons.

Similarly, of the four patients whose RBF fell below baseline at any time during the protocol, two maintained stable renal function. Thus, there is no predictable relationship between radiocontrast-associated global renal vasoconstriction and RCIN in this high-risk population.

While most animal investigations of the renal hemodynamic effects of CM have shown vasodilation followed by vasoconstriction of variable duration [13–16, 35, 36] this finding is not universal. Indeed, two separate studies using an electromagnetic flow probe to measure RBF in dogs showed a tendency for RBF to rise following CM injection [23, 29]. Furthermore, a recent study in pigs in which RBF was measured by renal vein thermodilution catheter demonstrated no change in RBF after high-dose ionic or non-ionic CM injection [37].

Prior human studies of the renal hemodynamic effects of CM are few and equivocal. When RBF was measured by Xenon washout no effect on RBF was discernible 30 minutes after aortography [25]. Using a dye-dilution method, Aperia, Broberger and Ekengren reported a significant decline in RBF one minute after renal arteriography in five children, four of whom had CRF [24]. Other studies in humans employing PAH clearance or extraction to estimate RBF have shown a decrease of variable duration after CM injection [21, 38, 39]. However, hippurate may not be a valid tool for estimating RBF in the presence of iodinated CM. CM immediately decreases renal PAH extraction in humans [19, 20] and dogs [12, 23, 40], a reversible effect which can be dissociated from changes in RBF and which probably represents a direct inhibition of tubular transport [22].

Thus, neither in animals nor much less in humans is the renal vasoconstrictive effect of CM established. Our results suggest quite the contrary: that CM injection is not associated with diminished total RBF in humans.

Global renal vasoconstriction has figured prominently in the proposed pathogenesis of RCIN based largely on circumstantial evidence from animal experiments [10, 11]. The difficulty in establishing a causal relationship between renal vasoconstriction and renal failure has resulted from the remarkable resistance of experimental animals to radiocontrast-induced renal failure. Four animal models of RCIN now exist [26–29] and three have been used to explore the pathogenic role of renal vasoconstriction. Lund et al were unable to demonstrate a correlation between degree of pathologic damage and the contrast-induced decrease in RBF in a canine preparation [26]. In rabbits with established RCIN, RBF was no different from a control group. The immediate renal hemodynamic effects of CM were not assessed in that study [27]. Finally, Margulies et al found no decline in RBF after intra-aortic injection of CM; indeed, there was a tendency for RBF to increase during the CM infusion [29].

In summary, no previous animal studies have shown a pathogenic role for global renal vasoconstriction in RCIN. No previous studies in humans have explored the question. The present data suggest that the development of RCIN in humans is not dependent on global renal vasoconstriction and conversely, that renal vasoconstriction following CM injection does not necessarily predispose to RCIN in high-risk patients.

Nine of the 12 patients we studied were taking calcium channel blockers on a long-term basis at the time of the protocol. The evidence that calcium channel blockers may prevent RCIN in humans is equivocal [6, 41, 42]. In the present study, five of the six patients who developed RCIN were taking

calcium channel blockers. S_{Cr} remained stable in two of the three patients taking no calcium channel blocker. Nonetheless, our sample size is too small to assess the statistical significance of any effect of calcium channel blockers on the development of RCIN.

In the setting of normal renal function, an acute dose of a calcium channel blocker may mitigate the CM-associated renal hemodynamic effects seen by some investigators [21, 43, 44]. However, patients with renal impairment appear to be largely resistant to the renal vasodilatory effect of an acute i.v. dose [45] or long-term administration [45–50] of calcium channel blockers. Whether these drugs, given long-term, might modify the renal hemodynamic response to CM in patients with renal impairment has not been addressed systematically in prior studies, nor in the present study. In our population, of the three patients taking no calcium channel blockers, none had a fall in RBF below baseline at any time during the cardiac catheterization.

Irrespective of any possible confounding effect of calcium channel blockers on renal hemodynamics, the present study strongly suggests that global renal vasoconstriction does not have a pathogenic role in human RCIN. Only two of the six patients who developed RCIN had even a transient decrease, and none had a sustained decrease, in RBF during the catheterization (Fig. 6).

The results of our study do not argue against a role for renal ischemia in the pathogenesis of RCIN. CM infusion may result in intrarenal redistribution of RBF leading to medullary ischemia undetectable by measurements of global RBF. Such a mechanism is suggested by the multiple-insult rat model of RCIN in which pathologic injury is confined largely to the outer medulla [28], a region of the kidney on the verge of anoxia under normal circumstances [51]. Measurement of regional RBF by laser Doppler flowtometry during CM infusion into rats shows a shift of blood flow from the medulla to the cortex [52], supporting this mechanism. A deleterious effect of CM injection on medullary blood flow is further supported by a recent study showing that radiocontrast-induced pathologic and functional damage in rats may be modulated by manipulating the nitric oxide system, which appears to participate in the regulation of medullary blood flow and oxygen balance [53]. Further emphasizing that CM-induced damage may result from an imbalance of medullary oxygen supply and consumption is the observation that furosemide mitigates medullary injury in the rat model of RCIN [54], presumably by decreasing medullary oxygen consumption. Two studies in humans examining RBF redistribution following CM injection have yielded conflicting results [25, 55].

In summary, intracardiac injection of ionic CM is not associated with a fall in global RBF in most patients with chronic renal failure. Furthermore, there appears to be no relationship between the development of acute RCIN and any change in global RBF. Additional studies are needed to define the pathogenic role of intrarenal redistribution of blood flow and renal oxygen economy in humans.

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